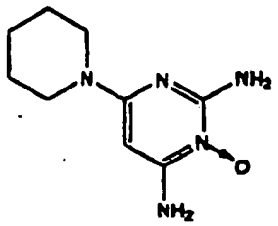
MINOXIDIL-BASED COMPOSITION FOR HAIR

The invention relates to a Minoxidil-based composition for hair to stimulate growth of keratinocytes[1] and promote hair regrowth.

Today it is well known, in particular from US patent 4 139 619, that external topical use of Minoxidil makes it possible, by treating the scalp, to stop hair loss and to enable hair regrowth. Considerable clinical research has demonstrated the benefit of such a product, and several commercial preparations have been marketed to date.

The use of Minoxidil, or 6-(1-piperidinyl)-2,4-pyrimidinediamine-3-oxide, of formula:



has a major drawback. Since the solubility of Minoxidil in water is quite low, it is actually necessary to use low-polarity solvents to dissolve this molecule.

The aforementioned US patent suggested using solvents of the glycol type, such as propylene glycol or polyethylene glycol, or solvents of the N-methyl pyrrolidone type.[2]

Formulas have also been described that use emulsion type vehicles where Minoxidil is either dissolved or dispersed as a solution in more lipophilic products, such as sorbitan esters or ethoxylated fatty alcohols.

Ointments also exist that combine Minoxidil with fatty substances such as lanolin, paraffin oils, and vaseline [white petrolatum].

Quite clearly these products are very difficult to use, since their use on the scalp is quite unpleasant and patients refuse to use such greasy products.

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[1] Translator's Note: Corrected French misprint "kéranocytes", should be "kératinocytes."
[2] Translator's Note: Corrected French misprint "pyrolidone", should be "pyrrolidone."

With the aim of improving these formulations, formulations have been suggested that combine ethyl or isopropyl alcohol with solvents of molecular weight ranging from 200 to 600, such as propylene glycol or polyethylene glycol, N-methylpyrrolidone, or diethylene glycol monoethyl ether. These solvents in combination make it possible to solubilize Minoxidil and to ensure its stability over time. However, these formulations still contain significant doses of propylene glycol (30%).

It is well known that despite the motivation of the user, even lotions combining ethyl alcohol and propylene glycol, which are considered as the least unpleasant products, will be abandoned since the hair quickly becomes greasy and shiny, with an unaesthetic appearance.

An obvious solution would be to replace the polyalcohol with another alcohol, but formulation of an ethyl alcohol/water lotion leads to insolubility of 2% Minoxidil in a 50/50 mixture.

Compared with conventional lotions that use alcohol/polyalcohol combinations, the aim of this invention is to prepare a hair lotion that is pleasant to use while utilizing a much smaller quantity of polyalcohol, in particular propylene glycol.

The composition for hair according to the invention is characterized in that it contains:

0.1% to 3% by weight Minoxidil,
0.1% to 3% by weight cyclodextrin,
0.5% to 10% by weight of a solvent for Minoxidil,
30% to 50% by weight of an alcohol,
water to make up 100%.

According to another aspect of this invention, the amount of cyclodextrin present in the composition for hair is such that it permits a substantial reduction in the amount of solvent for Minoxidil which would normally need to be added to achieve a comparable solubility of Minoxidil in the absence of the aforementioned cyclodextrin.

Cyclodextrins suitable for use in preparing the compositions for hair according to the invention are well known. An exhaustive list can be found in several documents available to the person skilled in the art.

Among the cyclodextrins that are advantageously used within this invention, we might mention cyclodextrins selected from among α-cyclodextrins, β-cyclodextrins, partially methylated β-cyclodextrins, and hydroxypropyl-β-cyclodextrins, singly or mixed. The α-cyclodextrins are soluble in water at a concentration of about 12.7%, β-cyclodextrins are soluble at about 1.8%, and partially methylated β-cyclodextrins are soluble at about 68%.

Cyclodextrins, singly or mixed, with solubility in water greater than 6% are preferably selected.

Partially methylated β-cyclodextrins are preferred for the compositions according to the invention.

The solvents for Minoxidil are those which are generally known to have such a property, i.e., glycol derivatives or N-methylpyrrolidone or diethylene glycol monoethyl ethers.

We might mention as an indicative list of glycol derivatives: propylene glycol, ethylene glycol, dipropylene glycol, and generally any polyethylene glycol with molecular weight ranging from 200 to 600.

Propylene glycol is nevertheless the preferred glycol for preparation of compositions according to the invention.

The composition preferably contains from 2% to 8% of solvent for Minoxidil.

Among the alcohols, which are in fact monoalcohols, we might mention C_2-C_4 alcohols and in particular ethyl alcohol or isopropyl alcohol.

In trials with patients using different lotions according to this invention, it was found that the compositions for hair according to the invention have particularly attractive properties after application with regard to the following three features:

- nongreasy appearance,
- drying time of about 5 minutes,
- easy styling.

In addition, 30 minutes after application, the hair has a natural appearance, i.e., the hair is "nongreasy", full-bodied and not dull, and is soft and easy to style.

The day after application, this same appearance was completely preserved.

The invention also relates to a process for cosmetic treatment of alopecia, involving application of a daily effective dose of Minoxidil in the form of a composition such as has been described above.

Compositions according to the invention are prepared by mixing the different ingredients, and more precisely by dissolving Minoxidil in the alcohol phase and then adding the cyclodextrin(s), the aforementioned solvent for Minoxidil, and finally water.

The lotion obtained is clear, pleasant to use, nongreasy, and nonsticky.

In order to achieve rapid drying of the composition and the best possible tolerance, the composition should preferentially have an alcohol content less than 55% by volume.

The examples below illustrate the invention but do not limit it.

Example 1

By dissolving Minoxidil in 95[%] v/v ethanol and then adding the other ingredients, a composition comprising the following is prepared:

- Minoxidil 2 g
- β-cyclodextrin (PMCD) 1 g
- 95[%] v/v ethyl alcohol 42.3 g
- Propylene glycol 5 g
- Purified water to make up 100 mL

PMCD: partially methylated cyclodextrin.

Example 2

The following composition is prepared by the procedure of Example 1:

- Minoxidil 1 g
- β-cyclodextrin (PMCD) 1 g
- 95[%] v/v ethyl alcohol 40 g
- Propylene glycol 10 g
- Purified water to make up 100 mL

Example 3

The following composition is prepared by the procedure of Example 1:

- Minoxidil 1 g
- α-cyclodextrin 0.5 g
- Propylene glycol 1 g
- 95[%] v/v ethyl alcohol 42 g
- Purified water to make up 100 mL

Example 4

The following composition is prepared by the procedure of Example 1:

- Minoxidil 2 g
- β-cyclodextrin (PMCD) 1 g
- Propylene glycol 2 g
- 95[%] v/v ethyl alcohol 42.3 g
- Purified water to make up 100 mL

Example 5

The following composition is prepared by the procedure of Example 1:

- Minoxidil 2 g
- Hydroxypropyl-β-cyclodextrin 1 g
- Propylene glycol 2 g
- 95[%] v/v ethyl alcohol 42.3 g
- Purified water to make up 100 mL

Example 6 (comparative)

The following composition is prepared by the procedure of Example 1:

- Minoxidil 2 g
- 95[%] v/v ethyl alcohol 30 g
- Propylene glycol 30 g
- Purified water to make up 100 mL

Example 7 - Trial on scalp

The aim of the comparative experiments below was to comparatively assess the cosmetic acceptability and efficacy of the hair lotion compositions of Examples 1 to 6.

The single-center double-blind and randomized trial was conducted in a specialized center with 12 male subjects using half-head tests.

· The trial lasted 8 days.

· The amount of the composition applied per half-head was 0.5 mL.

The compositions of Examples 1 to 5 had a drying time of about five minutes, and were shown to be satisfactory regarding nongreasy appearance and easy styling of the hair. Thus 30 minutes after application, the hair had a natural appearance, was full-bodied and "nongreasy", was not dull, and was soft and easy to style.

· The day after the applications, the hair remained "nongreasy", "not limp", full-bodied, and was soft, shiny, and easy to style, with a natural appearance.

The composition of Example 1 was shown to be the most attractive compared to the other three tested compositions.

The problems encountered with the composition of Example 6 were as follows:

· Drying time longer than 30 minutes.

· "Greasy" appearance of the hair.

The compositions of the examples according to the invention, for equal quantities of Minoxidil, were shown to be as effective as the same compositions of the prior art.

CLAIMS

1. Composition for hair to stimulate growth of keratinocytes and to promote hair regrowth, characterized in that it contains:

0.1% to 3% by weight Minoxidil,
0.1% to 3% by weight cyclodextrin,
0.5% to 10% by weight of a solvent for Minoxidil,
30% to 50% by weight of an alcohol,
water to make up 100%.

2. Composition according to Claim 1, characterized in that it contains from 2% to 8% by weight of a solvent for Minoxidil.

3. Composition according to Claim 1 or Claim 2, characterized in that it contains between 0.5% and 2% Minoxidil.

4. Composition according to Claim 1 to Claim 3, characterized in that the aforementioned cyclodextrin is selected from among α-cyclodextrins, β-cyclodextrins, partially methylated β-cyclodextrins, and hydroxypropyl-β-cyclodextrins, singly or mixed.

5. Composition according to Claim 4, characterized in that the aforementioned cyclodextrin is selected from among partially methylated β-cyclodextrins.

6. Composition according to any one of Claims 1 to 5, characterized in that the alcohol is selected from among ethyl alcohol and isopropyl alcohol.

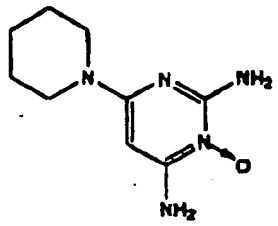
7. Composition according to any one of Claims 1 to 6, characterized in that the solvent for Minoxidil is selected from among polyethylene glycols of molecular weight ranging from 200 to 600, preferably propylene glycol.

MINOXIDIL-BASED COMPOSITION FOR HAIR WITH LOW FATTY SOLVENT CONTENT

The invention relates to a Minoxidil-based composition for hair, containing a small amount of greasy solvent, to stimulate growth of keratinocytes[1] and promote hair regrowth.

Today it is well known, in particular from US patent 4 139 619, that external topical use of Minoxidil makes it possible, by treating the scalp, to stop hair loss and to enable hair regrowth. Considerable clinical research has demonstrated the benefit of such a product, and several commercial preparations have been marketed to date.

The use of Minoxidil, or 6-(1-piperidinyl)-2,4-pyrimidinediamine-3-oxide, of formula:



because of its very low solubility in aqueous medium, must be combined with a mixture of low-polarity solvents in order to make possible excellent solvation and good penetration to the hair bulb.

The aforementioned US patent suggested using solvents of the glycol type, such as propylene glycol or polyethylene glycol, or solvents of the N-methyl pyrrolidone type.[2] These nonvolatile products make it possible to keep the active ingredient in solution and to ensure good penetration.

Formulas have also been described that use emulsion type vehicles where Minoxidil is either dissolved or dispersed as a solution in more lipophilic products, such as sorbitan esters or ethoxylated fatty alcohols.

Ointments also exist that combine Minoxidil with fatty substances such as lanolin, paraffin oils, and vaseline [white petrolatum].

However, these solvents make the hair greasy and unaesthetic in appearance, and it is quite clear that these formulations are very difficult to use, since their use on the scalp is quite unpleasant.

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[2] Translator's Note: Corrected French misprint "pyrolidone", should be "pyrrolidone."

When users apply these lotions long term, they end up discontinuing the treatment because whether or not the results in the area of regrowth are remarkable, the oily and unaesthetic appearance of the hair make them give up the treatment or at least use the lotion less frequently and of course they lose the benefits of the treatment.

With the aim of improving these formulations, formulations have been suggested that combine ethyl or isopropyl alcohol with solvents of molecular weight ranging from 200 to 600, such as propylene glycol or polyethylene glycol, N-methylpyrrolidone, or diethylene glycol monoethyl ether. These solvents in combination make it possible to solubilize Minoxidil and to ensure its stability over time. However, these formulations still contain significant doses of propylene glycol (30%).

It is well known that despite the motivation of the user, even lotions combining ethyl alcohol and propylene glycol, which are considered as the least unpleasant products, will be abandoned since the hair quickly becomes greasy and shiny, with an unaesthetic appearance.

An obvious solution would be to replace the polyalcohol with another alcohol, but formulation of an ethyl alcohol/water lotion leads to insolubility of 2% Minoxidil in a 50/50 mixture.

We might also mention the patent application WO-A-95/25500 published 28 September 1995, relating to a composition for hair containing:

0.1% to 3% by weight Minoxidil,
0.1% to 3% by weight cyclodextrin,
0.5% to 10% by weight of a solvent for Minoxidil,
30% to 50% by weight of an alcohol,
water to make up 100%.

The explicitly mentioned cyclodextrins are α-cyclodextrins, β-cyclodextrins, partially methylated β-cyclodextrins, and hydroxypropyl-β-cyclodextrins, singly or mixed.

Compared with conventional lotions that use alcohol/polyalcohol combinations, the aim of this invention is to prepare a hair lotion that is pleasant to use while using a much lower amount of polyalcohol, in particular propylene glycol.

It has now been discovered that Minoxidil-based compositions for hair including a γ-cyclodextrin as the cyclodextrin could replace those compositions including the cyclodextrins mentioned

in the aforementioned patent application WO-A-95/25500.

The composition for hair according to the invention is characterized in that it contains:

0.1% to 7% by weight Minoxidil,
0.1% to 5% by weight of a γ-cyclodextrin,
0.5% to 15% by weight of a solvent for Minoxidil,
30% to 50% by weight of a monoalcohol,
water to make up 100%.

According to another aspect of this invention, the amount of γ-cyclodextrin present in the composition for hair is such that it permits a substantial reduction in the amount of solvent for Minoxidil which would normally need to be added to achieve a comparable solubility of Minoxidil in the absence of the aforementioned cyclodextrin.

By γ-cyclodextrin, we mean in particular natural cyclic compounds consisting of 8 (γ) (1→4)-D-glucopyranoside units, either in unsubstituted or substituted form, for example substituted by amino or carboxy groups. The γ-cyclodextrins can be present singly or mixed.

The unmodified γ-cyclodextrin with solubility in water in particular on the order of 23% is preferred.

The solvents for Minoxidil are those which are generally known to have such a property, i.e., glycol derivatives or N-methylpyrrolidone or diethylene glycol monoethyl ethers.

We might mention as an indicative list of glycol derivatives: propylene glycol, ethylene glycol, dipropylene glycol, and generally any polyethylene glycol with molecular weight ranging from 200 to 600.

Propylene glycol is nevertheless the preferred glycol for preparation of compositions according to the invention.

Among the monoalcohols, we might mention C_2-C_4 alcohols and in particular ethyl alcohol or isopropyl alcohol.

In a first variant, the composition for hair according to the invention is characterized in that it contains:

0.1% to 3% by weight Minoxidil,
0.1% to 3% by weight of a γ-cyclodextrin,
0.5% to 10% by weight of a solvent for Minoxidil,
30% to 50% by weight of a monoalcohol,
water to make up 100%.

The composition preferably contains from 2% to 8% of solvent for Minoxidil.

The composition also preferably contains from 0.5% to 2.5% by weight Minoxidil.

In a second variant, the composition for hair according to the invention is characterized in that it contains:

3% to 7% by weight Minoxidil,

2% to 5% by weight of a γ-cyclodextrin,

5% to 15% by weight of a solvent for Minoxidil,

30% to 50% by weight of a monoalcohol,

water to make up 100%.

The composition preferably contains from 8% to 12% by weight of a solvent for Minoxidil.

The composition also preferably contains from 4% to 6% by weight Minoxidil.

In trials with patients using different lotions according to this invention, it was found that the compositions for hair according to the invention had particularly attractive properties after application with regard to the following three features:

- nongreasy appearance,
- drying time of about 5 minutes,
- easy styling.

In addition, 30 minutes after application, the hair had a natural appearance, i.e., the hair was "nongreasy" and full-bodied, not dull, and was soft and easy to style.

The day after the applications, this same appearance was completely preserved.

The invention also relates to a process for cosmetic treatment of alopecia, involving application of a daily effective dose of Minoxidil in the form of a composition such as has been described above.

Compositions according to the invention are prepared by mixing the different ingredients, and more precisely by dissolving Minoxidil in the alcohol phase and then adding the γ-cyclodextrin, the aforementioned solvent of Minoxidil, and finally water.

The lotion obtained is clear, pleasant to use, nongreasy, and nonsticky.

In order to achieve rapid drying of the composition and the best possible tolerance, the composition should preferentially have an alcohol content less than 55% by volume.

The examples below illustrate the invention but do not limit it.

Example 1

By dissolving Minoxidil in 95[%] v/v ethanol and then adding the other ingredients, a composition comprising the following is prepared:

- Minoxidil 2 g
- β-cyclodextrin (unmodified) 1 g
- 95[%] v/v ethyl alcohol 42.3 g
- Propylene glycol 5 g
- Purified water to make up 100 mL
- The γ-cyclodextrin has a solubility in water of 23%.

Example 2

The following composition is prepared by the procedure of Example 1:

- Minoxidil 1 g
- β-cyclodextrin (unmodified) 1 g
- 95[%] v/v ethyl alcohol 40 g
- Propylene glycol 10 g
- Purified water to make up 100 mL
- The γ-cyclodextrin has a solubility in water of 23%.

Example 3

The following composition is prepared by the procedure of Example 1:

- Minoxidil 5 g
- γ-cyclodextrin (unmodified) 3 g
- 95[%] v/v ethyl alcohol 42 g
- Propylene glycol 10 g
- Purified water to make up 100 mL
- The γ-cyclodextrin has a solubility in water of 23%.

Example 4 (comparative)

The following composition is prepared by the procedure of Example 1:

· Minoxidil	2 g
· 95[%] v/v ethyl alcohol	30 g
· Propylene glycol	30 g
· Purified water to make up	100 mL

Example 5 - Trial on scalp

The aim of the comparative experiments below was to comparatively assess the cosmetic acceptability and efficacy of the hair lotion compositions of Examples 1 to 4.

The single-center double-blind and randomized trial was conducted in a specialized center with 12 male subjects using half-head tests.

· The trial lasted 8 days.

· The amount of the composition applied per half-head was 0.5 mL.

The compositions of Examples 1, 2 and 3 had a drying time of about five minutes, and were shown to be satisfactory regarding nongreasy appearance and easy styling of the hair. Thus 30 minutes after application, the hair had a natural appearance, was full-bodied and "nongreasy", was not dull, and was soft and easy to style.

· The day after the applications, the hair remained "nongreasy", "not limp", full-bodied, and was soft, shiny, and easy to style, with a natural appearance.

The compositions of Examples 1 and 3 were shown to be the most attractive compared to the other three tested compositions.

The problems encountered with the composition of Example 4 were as follows:

· Drying time longer than 30 minutes.

· "Greasy" appearance of the hair.

The compositions of the examples 1, 2 and 3 according to the invention, for equal quantities of Minoxidil, were shown to be as effective as the same compositions of the prior art.

CLAIMS

1. Composition for hair to stimulate growth of keratinocytes and to promote hair regrowth, characterized in that it contains:

0.1% to 7% by weight Minoxidil,
0.1% to 5% by weight of a γ-cyclodextrin,
0.5% to 15% by weight of a solvent for Minoxidil,
30% to 50% by weight of a monoalcohol,
water to make up 100%.

2. Composition according to Claim 1, characterized in that it contains:

0.1% to 3% by weight Minoxidil,
0.1% to 3% by weight cyclodextrin,
0.5% to 10% by weight of a solvent for Minoxidil,
30% to 50% by weight of an alcohol,
water to make up 100%.

3. Composition according to Claim 2, characterized in that it contains from 2% to 8% by weight of a solvent for Minoxidil.

4. Composition according to Claim 2 or Claim 3, characterized in that it contains between 0.5% and 2.5% by weight Minoxidil.

5. Composition according to Claim 1, characterized in that it contains:

3% to 7% by weight Minoxidil,
2% to 5% by weight of a γ-cyclodextrin,
5% to 15% by weight of a solvent for Minoxidil,
30% to 50% by weight of a monoalcohol,
water to make up 100%.

6. Composition according to Claim 5, characterized in that it contains from 8% to 12% by weight of a solvent for Minoxidil.

7. Composition according to any one of Claims 5 or 6, characterized in that it contains between 4% and 6% by weight Minoxidil.

8. Composition according to any one of the preceding claims, characterized in that the γ-cyclodextrin is unmodified.

9. Composition according to any one of the preceding claims, characterized in that the monoalcohol is selected from the group comprising ethyl alcohol and isopropyl alcohol.

10. Composition according to any one of the preceding claims,

characterized in that the solvent for Minoxidil is selected from among polyethylene glycols of molecular weight ranging from 200 to 600.

11. Composition according to Claim 11, characterized in that the solvent for Minoxidil is propylene glycol.